REMARKS

Applicant respectfully requests reconsideration. Claims 1-3, 7-9, 26-30, and 33 were previously pending in this application. Claim 7 has been cancelled. Claim 1 has been amended. Support for the amendment may be found, for example, in claim 7. Claims 1-3, 8-9, 26-30, and 33 remain pending with claims 1, 28, and 33 being independent. No new matter has been added.

Status of Claim 33

The status of claim 33 is unclear. The Examiner appears to have withdrawn the claim from examination as "being directed towards a previously cancelled claim", but rejects the claim under 35 U.S.C. §103(a) (see below). At the outset, it is believed that withdrawal of the claim as being directed towards a previously cancelled claim is improper. The scope of claim 33 is consistent with that of previously pending claim 32, which was examined in this application without restriction. Accordingly, claim 33 should be examinable in this application and thus, Applicant has addressed the rejections to claim 33 below.

Rejection of Claims 1-3, 7-9, 26-30 and 33 under 35 U.S.C. §103(a)

Claims 1-3, 7-9, 26-30, and 33 are rejected under 35 U.S.C. §103(a) as being unpatentable over European Patent Application No. 0207696 ("Leguzza") in view of Solomons et al., Organic Chemistry, 2008, 9th Edition, John Wiley & Sons, Inc., page 224-236 ("Solomons").

Applicant respectfully requests reconsideration. The Office Action states that an artisan of ordinary skill would have been motivated to make the alpha-iodoketone of the present invention in place of the alpha-bromoketone of Leguzza, because Solomons teaches that iodine is a better leaving group than bromine. The Office Action further states that one of ordinary skill in the art would have been motivated to convert the alpha-haloketone to the desired product to both increase the yield of the reaction and obtain the desired product via a more facile method having one less synthetic step than the process described in Leguzza.

As Applicant has outlined in previous responses, Applicant sees no motivation or suggestion in Leguzza or Solomons to combine the teachings of Leguzza and Solomons in the manner stated in the Office Action. One of ordinary skill in the art would not have been motivated to combine the

teaching in the Leguzza application with the teaching in Solomons in the manner stated in the Office Action. By contrast, those of ordinary skill in the art would expect that the use of iodine in the Leguzza process would produce an alpha-iodoketone that is highly unstable, relative to the corresponding alpha-bromoketone, increasing the risks of side reactions, including Favorskii rearrangements, as described in previous responses. Those of ordinary skill in the art would also expect that the alpha-iodoketone intermediate could not be isolated. Thus, there would be no reasonable expectation of success in modifying the process of Leguzza with the teaching of Solomons.

Nonetheless, without conceding the merits of the rejection but in order to expedite allowance, and hereby expressly reserving the right to prosecute the original (or similar) claim scope as encompassed by claim 1 as previously pending, claim 1 has been amended to recite that one of R^1 and R^2 is hydrogen and the other of R^1 and R^2 is *n*-propyl. Independent claims 28 and 33 comprise a similar limitation in that substituents on the nitrogen atom are hydrogen and *n*-propyl. In the process described in the Leguzza application, both R^1 and R^2 are alkyl. As will be understood by those of ordinary skill in the art, when at least one of R^1 of R^2 is hydrogen, unexpected side reactions may occur, for example, irreversible nucleophilic attack by the nitrogen, resulting in a loss of the hydrogen. The unexpected side reactions are in addition to those described above which would be expected by one of ordinary skill in the art when using iodine in the Leguzza process. Thus, those of ordinary skill in the art would not be motivated to or expect success when replacing at least one of R^1 or R^2 with hydrogen.

In addition, as described in previously filed responses, an unexpected advantage of the process of the present invention is that it allows the conversion to be performed *in situ*, i.e. without isolation of the alpha-haloketone intermediate. The process in the Leguzza application requires the use of glacial acetic acid, hydrogen bromide, and bromine. Those of ordinary skill in the art would expect a high risk of these reagents interfering with the cyclisation reaction with the thiourea if they were not removed. Accordingly, it follows that this is the reason the intermediate alpha-bromoketone was isolated in the process of the Leguzza application. In contrast, the use of iodine alone surprisingly resulted in reaction conditions that allowed for the halogenation of the ketone, yet were sufficiently mild to avoid substantial interference with the cyclisation process, therefore

avoiding the need to isolate the alpha-iodoketone intermediate. Accordingly the process of the present invention may be performed in a much simpler manner than that of the process described in Leguzza, with consequent significant cost savings on an industrial scale. Overall therefore it can be seen that the present invention is significantly higher yielding and more straightforward to perform than the process described in Leguzza.

Furthermore, the long time lapse (15+ years) between Leguzza and the filing date of the present application without any other reference disclosing the substitution of iodine for bromine in the process of Leguzza is further evidence of the inventiveness of this concept. Certainly, during this time period, much work had been done in the art to examine different synthetic routes to the products. Indeed, one aspect of the present invention is the realization that iodine could be used as a substitute for bromine.

Because each claim limitation is not taught or suggested by Leguzza or Solomons, and there is no articulated reasoning as to why one of ordinary skill in the art would modify the teachings of Leguzza and/or Solomons to predictably reach the invention as claimed, claims 1, 28, and 33 are patentable over Leguzza and Solomons. Claims 2-3, 8-9, and 26-27, and claims 29-30 depend from claim 1 and claim 28, respectively, and, thus, are also patentable over Leguzza and Solomons, for at least this reason.

Regarding claim 33, as noted above, the scope of claim 33 is consistent with that of previously pending claim 32, which was examined in this application without restriction. Previously pending claim 32 was rejected under 35 U.S.C. §103(a) as being unpatentable over Yokum et al., Tet. Lett. 1997, 38, 4013-4016 ("Yokum"), and also appears to be rejected on the above ground (although this is not completely clear, as the Patent Office indicated that claim 33 is not examined). Accordingly, outstanding rejections applied to previously pending claim 32, is now addressed.

Currently pending claim 33 is directed towards an intermediate useful in the process as claimed in claims 1 and 28. Yokum discusses the synthesis of a series of cyclohexyl based α,α-disubstituted amino acids for incorporation into peptides. It relates in no way to the synthesis of pramipexole in particular or 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles in general. Thus on reading Yokum, one of ordinary skill in the art would have no reason to think that the compounds

disclosed therein might be useful as intermediates in the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles such as pramipexole.

Furthermore the Examiner has alleged that just because Yokum discloses compounds of formula **2a** in which R^1 is hydrogen and R^2 is ethyl or butyl, it would be obvious to prepare the allegedly homologous n-propyl derivative of claim 33. This is not the case.

Yokum discloses not only compounds in which R^2 is ethyl or butyl, but also compounds in which R^2 is benzyl or 2-napthylmethyl (see page 4014). The purpose of synthesising these compounds is simply to demonstrate that the reductive amination can be performed so as to introduce a wide variety of R^2 groups (see the sentence spanning pages 4013 and 4014). Accordingly, even if one of ordinary skill in the art were to seek to synthesise a compound of formula **2a** with an alternative R^2 group, then on reading Yokum one of ordinary skill in the art would be faced with a bewildering array of groups to choose from. Yokum provides no incentive whatsoever to synthesise compounds in which R^2 is propyl, let alone those in which R^2 is n-propyl as claimed in claim 33.

It is further noted that Yokum does not specify the nature of the butyl group (i.e. n-, sec-, iso- or tert-butyl). Thus the ethyl and butyl groups disclosed in Yokum cannot be seen as part of a homologous series with the n-propyl of claim 33 as alleged by the Examiner.

Because each claim limitation is not taught or suggested by Yokum, and there is no articulated reasoning as to why one of ordinary skill in the art would modify the teaching of Yokum to predictably reach the invention as claimed, claim 33 is patentable over Yokum.

Accordingly, withdrawal of the rejection of claims 1-3, 7-9, 26-30, and 33 is respectfully requested.

CONCLUSION

If, for any reason, the Examiner is of the opinion that prosecution would be expedited via a telephone conversation with the Applicant's representative, the Examiner is kindly invited to contact the undersigned at (617) 646-8000.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 23/2825.

Dated: 4/2/10

Respectfully submitted,

By _____
Robert H. Walat
Registration No.: 46,324
Timothy J. Oyer, Ph.D.
Registration No.: 36,628
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
617.646.8000